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23914	7590	09/09/2004	EXAMINER	
STEPHEN B. DAVIS BRISTOL-MYERS SQUIBB COMPANY PATENT DEPARTMENT P O BOX 4000 PRINCETON, NJ 08543-4000			ROBINSON, BINTA M	
			ART UNIT	PAPER NUMBER
			1625	
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Please find below and/or attached an Office communication concerning this application or proceeding.

219.

Office Action Summary

Application No.

10/779,539

Applicant(s)

LU ET AL.

Examiner

Binta M Robinson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 is/are pending in the application.
- 4a) Of the above claim(s) 9 and 10 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 8 is/are rejected.
- 7) ☒ Claim(s) 1-7 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 4/24/2004
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: ____

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-8, drawn to the compound of formula I, and the pharmaceutical composition containing the said compound
- II. Claims 9-10, are drawn to methods of use for the compounds of the formula (I) classified in various subclasses of class 514.

In addition to an election of one of the above Groups, restriction is further required under 35 U.S.C. 121 as follows:

If Group II is elected then election of one of the following methods of use is required: for example,

- A. Method of treating acute infection,
 - B. Method of treating acute phase response,
 - C. Method of treating anorexia,
 - D. Method of treating asthma,
 - E. Method of treating autoimmune disease
 - F. Method of treating Bechet's disease,
- etc.

In accordance with the decisions in *In re Harnisch*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984), restriction of a Markush group is proper where the compounds within the group either (1) do not share a common utility, or (2) do not share a substantial structural feature

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disclosed as being essential to that utility. In addition, a Markush group may encompass a plurality of independent and distinct inventions where two or more members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the other member(s) obvious under 35 U.S.C. 103.

Where an election of Group I, is made, an election of a single compound is further required including an exact definition of each substitution on the base molecule (Formula (I)), wherein a single member at each substituent group or moiety is selected. For example, if a base molecule has a substituent group R1, wherein R1 is recited to be any one of H, OH, COOH, aryl, alkoxy, halogen, amino, etc., then applicant must select a single substituent f R1, for example OH or aryl and each subsequent variable position. In the instant case, upon election of a single compound, the Office will review the claims and disclosure to determine the scope of the independent invention encompassing the elected compound (compounds which are so similar thereto as to be within the same inventive concept and reduction to practice). The scope of an independent invention will encompass all compounds within the scope of the claim, which fall into the same class and subclass as the elected compound, but may also include additional compounds, which fall in related subclasses. Examination will then proceed on the elected compound AND the entire scope of the invention encompassing the elected compound as defined by common classification. A clear statement of the examined invention, defined by those class(es) and subclass(es) will be set forth in the first action on the merits. Note that the restriction requirement will not be made final until such time

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as applicant is informed of the full scope of compounds along with (if appropriate) the process of using or making said compound under examination. This will be set forth by reference to specific class(es) and subclass(es) examined. Should applicant traverse on the ground that the compound are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the compound to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other.

All compounds falling outside the class(es) and subclass(es) of the selected compound and any other subclass encompassed by the election above will be directed to nonelected subject matter and will be withdrawn from consideration under 35 U.S.C. 121 and 37 C.F.R. 1.142(b). Applicant may reserve the right to file divisional applications on the remaining subject matter. (The provisions of 35 U.S.C. 121 applies with regard to double patenting covering divisional applications.)

Applicant is reminded that upon cancellation of claims to a nonelected invention, the inventions must be amended in compliance with 37 C.F.R. 1.48(b) if one of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 C.F.R. 1.48(b) and by the fee required under 37 C.F.R. 1.17(i).

If desired upon election of a single compound, applicants can review the claims and disclosure to determine the scope of the invention and can **set forth** a group of compounds, which are so similar within the same inventive concept and reduction to

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practice. Markush claims must be provided with support in the disclosure for each member of the Markush group. See MPEP 608.01(p). Applicant should exercise caution in making a selection of a single member for each substituent group on the base molecule to be consistent with the written description.

Rationale Establishing Patentable Distinctiveness Within Each Group

Each Group listed above is directed to or involves the use of compounds which are recognized in the art as being distinct from one another because of their diverse chemical structure, their different chemical properties, modes of action, different effects and reactive conditions (MPEP 806.04, MPEP 808.01). Additionally, the level of skill in the art is not such that one invention would be obvious over the other invention (Group), i.e. they are patentable over each other. Chemical structures, which are similar, are presumed to function similarly, whereas chemical structures that are not similar are not presumed to function similarly. The presumption even for similar chemical structures though is not irrebuttable, but may be overcome by scientific reasoning or evidence showing that the structure of the prior art would not have been expected to function as the structure of the claimed invention. Note that in accordance with the holding of Application of Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and In re Lalu, 223 USPQ 1257 (Fed. Cir. 1984), chemical structures are patentably distinct where the structures are either not structurally similar, or the prior art fails to suggest a function of a claimed compound would have been expected from a similar structure.

The above groups represent general areas wherein the inventions are independent and distinct, each from the other because of the following reasons:

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Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be in a materially different process with as shown in claims 9-10.

In addition, because of the plethora of classes and subclasses in each of the Groups, a serious burden is imposed on the examiner to perform a complete search of the defined areas. Therefore, because of the reasons given above, the restriction set forth is proper and not to restrict would impose a serious burden in the examination of this application.

Advisory of Rejoinder

The following is a recitation of M.P.E.P. 821.04, Rejoinder:

Where product and process claims drawn to independent and distinct inventions are presented in the same application, applicant may be called upon under 35 U.S.C. 121 to elect claims to either the product or process. See MPEP § 806.05(f) and § 806.05(h). The claims to the nonelected invention will be withdrawn from further consideration under 37 CFR 1.142. See MPEP § 809.02(c) and § 821 through § 821.03. However, if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined.

Where the application as originally filed discloses the product and the process for making and/or using the product, and only claims directed to the product are presented for examination, when a product claim is found allowable, applicant may present claims directed to the process of making and/or using the patentable product by way of amendment pursuant to 37 CFR 1.121. In view of the rejoinder procedure, and in order to expedite prosecution, applicants are encouraged to present such process claims, preferably as dependent claims, in the application at an early stage of prosecution. Process claims which depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance. Amendments submitted after final rejection are governed by 37 CFR 1.116. Process claims which do not depend from or otherwise include the limitations of the patentable product will be withdrawn from consideration, via an election by original presentation (see MPEP § 821.03). Amendments submitted after allowance are governed by 37 CFR 1.312. Process claims which depend from or otherwise include all the limitations of an allowed product claim and which meet the requirements of 35 U.S.C. 101, 102, 103, and 112 may be entered.

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Where product and process claims are presented in a single application and that application qualifies under the transitional restriction practice pursuant to 37 CFR 1.129(b), applicant may either: (A) elect the invention to be searched and examined and pay the fee set forth in 37 CFR 1.17(s) and have the additional inventions searched and examined under 37 CFR 1.129(b)(2); or (B) elect the invention to be searched and examined and not pay the additional fee (37 CFR 1.129(b)(3)). Where no additional fee is paid, if the elected invention is directed to the product and the claims directed to the product are subsequently found patentable, process claims which either depend from or include all the limitations of the allowable product will be rejoined. If applicant chooses to pay the fees to have the additional inventions searched and examined pursuant to 37 CFR 1.129(b)(2) even if the product is found allowable, applicant would not be entitled to a refund of the fees paid under 37 CFR 1.129(b) by arguing that the process claims could have been rejoined. 37 CFR 1.26(a) states that "[T]he Commissioner may refund any fee paid by mistake or in excess of that required. A change of purpose after the payment of a fee...will not entitle a party to a refund of such fee..." In this case, the fees paid under 37 CFR 1.129(b) were not paid by mistake nor paid in excess, therefore, applicant would not be entitled to a refund. In the event of rejoinder, the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. If the application containing the rejoined claims is not in condition for allowance, the subsequent Office action may be made final, or, if the application was already under final rejection, the next Office action may be an advisory action. Form paragraphs 8.42 through 8.44 should be used to notify applicant of the rejoinder of process claims which depend from or otherwise include all the limitations of an allowable product claim.

In the event of rejoinder, the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104 - 1.106. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. If the application containing the rejoined claims is not in condition for allowance, the subsequent Office action may be made final, or, if the application was already under final rejection, the next Office action may be an advisory action.

The following is a recitation from paragraph five, "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. §103(b)" (1184 TMOG 86(March 26, 1996)):

"However, in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim **depends from or otherwise includes all the limitations of** an allowed product claim. Withdrawn process claims not commensurate in scope with an allowed product claim will not be rejoined." (emphasis added)

Therefore, in accordance with M.P.EP 821.04 and *In re Ochiai*, 71 F.3d 1565, 37 USPQ 1127 (Fed. Cir. 1995), rejoinder of product claims with process claims commensurate in scope with the allowed product claims will occur following a finding that the product claims are allowable. Until, such time, a restriction between product claims and process claims is deemed proper. Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process

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claims should be amended during prosecution to maintain either dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Response to Restriction

During a telephone conversation with Applicants' representative, Jing Belfield, on August 23, 2004, an election was made **with** traverse to prosecute **Group I**, claims 1-8, directed to products of Formula I, and the specific compound, example 159 on page 153 of the specification, is acknowledged.

As previously stated in the restriction requirement, in accordance with M.P.E.P. 821.04 and *In re Ochiai*, 71 F.3d 1565, 37 USPQ 1127 (Fed. Cir. 1995), rejoinder of product claims and method of use claims commensurate in scope with the allowed product claims will occur following a finding that the product claims are allowable. Until such time, a restriction between product claims and process is deemed proper.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Status of the Claims

Claims 1-10 are pending in this application. The unelected portion of claims 1-8 as well as claims 9-10 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention. The withdrawn subject

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matter is patentably distinct from the elected subject matter as it differs in structure and element and would require separate search considerations. In addition, a reference, which anticipates one group, would not render obvious the other.

The scope of the invention of the elected subject matter is as follows:

Compounds of formula I, depicted in claim 1, and the pharmaceutical composition wherein: wherein A is selected from is as claimed, B is piperidinyl, pyridinyl, Z is phenyl, naphthyl, and tetrahydronaphthyl substituted with 0-5 Rb, wherein Rb is as claimed, Ua is as claimed, Ya is as claimed, Za is quinolinyl, or pyridyl substituted with 0-5 Rc, Rc is as claimed except heterocycle, Rc1 is as claimed, R2 is as claimed, Q is as claimed except heterocycle, Q1 is as claimed except heterocycle, Rd is as claimed except heterocycle, Ra is as claimed, Ra1 is at each occurrence, independently is as claimed, Ra2 at each occurrence is independently as claimed, Rd are all moieties claimed except heterocycle, R5 at each occurrence is selected from C1-10 alkyl substituted with 0-2 Rb and C1-8 alkyl substituted with 0-2 Re; R3 at each occurrence is as claimed, p at each occurrence is selected from 0, 1, and 2, R3 is as claimed, Re is as claimed.

As a result of the election and the corresponding scope of the invention identified supra, the remaining subject matter of claims 1-8 as well as claims 9-10 are withdrawn from further consideration pursuant to 37 CFR 1.142 (b) as being drawn to non-elected inventions. The withdrawn compounds contain varying functional groups such as pyrimidinyl; imidazolyl, pyrrolidinyl etc, which are chemically recognized to differ in structure and function. This recognized chemical diversity of the functional groups can

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be seen by the various classification of these functional groups in the U.S. classification system, i.e.class 544 subclass 224(+) (diazines), class 546 subclass 184(+) (piperdines), 546 subclass 249(+) (pyridines) etc. Therefore the subject matter which are withdrawn from consideration as being non-elected subject differ materially in structure and composition and have been restricted properly a reference which anticipated but the elected subject matter would not even render obvious the withdrawn subject matter and the fields of search are not co-extensive.

Objections & Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,

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7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention in claim 8 is the a pharmaceutical composition containing the instant compound of formula I.

The State of the Prior Art

The state of the prior art is that metalloproteases are important in uncontrolled breakdown of connective tissue. This is a feature of many pathological conditions, such as rheumatoid and osteoarthritis, corneal, epidermal or gastric ulceration; tumor metastasis or invasion. Compounds which inhibit the productin of TNF are therefore of therapeutic importance for the treatment of inflammatory disorders. Recently, TNF-alpha converting enzyme, the enzyme responsible for TNF-alpha release from cells were purified and sequenced. (Black et. al., Nature 1997, 385, 729). .

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of TNF-mediated diseases, whether the TNF-alpha converting enzyme (TACE) was promoted or inhibited would affect the possible treatment of any disease.

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Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by the composition of claim 1 and the inhibition of TACE, one of skill in the art is unable to fully predict possible results from the administration of the composition of claim 8 due to the unpredictability of the role of TACE, i.e. whether promotion or inhibition would be beneficial for the treatment of the diseases.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present

The direction present in the instant specification is that the composition of claim 8 can inhibit the production of TNF which helps in the treatment of the claimed diseases. However, the specification is silent and fails to provide guidance as to whether the diseases listed as TNF-mediated diseases, require the inhibition of TACE or the promotion of TACE for treatment.

The presence or absence of working examples

There are no working examples for any diseases listed in the specification. Also, the compounds which are disclosed in the specification have no pharmacological data regarding the treatment of any other disease besides the rejection of an organ

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transplantation and have no data on the possible treatment of TNF-mediated diseases that require the promotion of TNF. Also, the specification fails to provide working examples as to how the listed diseases can be treated by the inhibition TNF, i.e. again, there is no correlation between the diseases listed and inhibition of TNF.

The breadth of the claims

The breadth of the claims is that the pharmaceutical composition of claim 8 can treat any of the diseases claimed in claims 9-10, without regards as to the affect of TNF on the stated diseases.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what listed diseases would be benefited by the inhibition of TACE and would furthermore then have to determine whether the claimed compounds would provide treatment of the disease by the inhibition of TACE.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the claim 1 for the treatment of an TACE-mediated disease. As a result necessitating one of skill to perform an exhaustive search for which NO-mediated

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diseases can be treated by the compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which NO-mediated diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome deleting the term "pharmaceutical" in line 1 of claim 8.

Claims 1-7 are objected to because they contain non-elected subject matter.

The IDS filed 4/28/04 has been considered.

The elected species is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562.

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A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

BMR
September 7, 2004


Cecilia J. Tsang
Supervisory Patent Examiner
Technology Center 1600